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(54) Title: MATRIX-ENTRAPPED BEADLET PREPARATION

(57) Abstract

This invention relates to a pharmaceutically acceptable preparation comprising one or more matrix-forming materials in which are entrapped particles which contain at least one beneficial agent.

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Matrix-entrapped Beadlet Preparation

Background of the Invention

This invention relates to solid, transparent or semi-transparent, pharmaceutically acceptable preparations (troches, lozenges) comprising one or more matrix-forming materials in which are entrapped small particles which contain at least one beneficial agent. This presentation interdicts tampering with the particles and their active agent and makes the preparations more tamper evident and tamper proof.

Introduction

Troches, also known as lozenges or pastilles, are disc-shaped solids containing a medical agent in a suitably flavored base. The base may be a hard sugar candy, glycerinated gelatin or the combination of sugar with sufficient mucilage to provide stability to a shape or form. These products are placed in the mouth where they slowly dissolve, liberating the active ingredient.

Troches can be prepared extemporaneously by a trained and licensed formulator. A classic method is to add water to a mixture of powdered drug, sugar and a gum until a pliable mass is obtained. This mass is shaped into roll and pieces are cut from this cane. Heat-stable compounds can be formulated into a hard candy base; such preparations are usually called lozenges. A sugar syrup, with or without a binder, is concentrated over heat until it becomes a pliable mass at which point the active is added and the mixture is kneaded while warm to form a homogeneous mass. This warm mass is then processed through a mold to give shape to product which is cooled thus forming the hard candy. Compression-based manufacturing has been used to prepare troches containing heat-labile ingredients.

This invention provides an advance in this art by providing a troche-like preparation as a carrier means for particulates, particularly beadlets, whereby the native condition of the beadlets can be observed through the matrix-forming material, in addition to the fact the integrity of the troche-like product can be observed at any point after manufacture or packaging.

Summary of the Invention

This invention comprises a pharmaceutically acceptable preparation comprising at least one pharmaceutically acceptable transparent or semi-transparent solid matrix-forming material in which are entrapped small particles which contain at least one beneficial agent.

In a second aspect, this invention relates to a process for manufacturing these products using injection molding.

Detailed Description of the Invention

The finished product is a pharmaceutical preparation comprising some type of matrix-forming, edible material in which are entrapped small particles which comprise or contain an

active agent. The matrix-forming material is some edible material which is a solid at ambient temperature and is transparent, or semi-transparent to a degree that is no greater than what allows the user to view some or all of the entrapped particles when viewed under normal lighting conditions by the naked eye. Lozenge and troche preparations are illustrations of preparations within the scope of this invention. The compositional make-up of troche and lozenge preparations can be found in such texts as Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Co., Easton, PA, USA, pp 1644-1665 (1990) and Sugar Confectionery Manufacture, E. B. Jackson, Ed. Van Nostrand Reinhold, New York, pp 245-247 (1990) for example.

As regards the matrix-forming materials, any materials known to the art which is edible, is solid at ambient temperature and is not plastic or malleable at that temperature, can act as a matrix for small particles, and allows viewing of the entrapped particles can be used in these preparations. The matrix may be formed using one compound, for example a wax or a sugar or a mixture of materials can be employed. Mixtures may comprise two or more materials from the same class of compounds, such as mixed sugars, or may be a mixture of compounds from two or more classes such as a sugar, a wax and a polyol. Where mixtures are used, they may be used in a way that causes them to retain their original identity, or they may be transformed during the manufacturing process to a second form representing a combining of subunits into a different chemical entity such as happens when polymerization or cross-linking occurs.

Preferred matrix-forming materials are sugars and edible waxes. Sugars such as sucrose, dextrose, fructose, sorbitol, lycasin and other simple and complex carbohydrates which can be used to form lozenges are preferred. Waxes such as white wax, gelucires, carnauba wax, hydrogenated vegetable oils, Labrafils, Compritol 888 ATO, Precirol, polyethylene glycols, bees wax, paraffins, microcrystalline wax, acetylated monoglycerides, cetyl alcohol, and glyceryl monostearate. White wax is a particularly preferred matrix-forming agent for use in this invention.

Matrices that can be formed using this invention can be of two types, disintegrating or non-disintegrating. Non-disintegrating matrices can be formed using hydrophoibic matrix-forming materials described above. Disintegrating matrices can be formed using a combination of hydrophilic and hydrophobic matrix forming materials; these are represented by the list of materials given above. The ratio of hydrophobic to hydrophilic materials can be adjusted to accomplish a desired disintegration time.

Besides using hydrophilic matrix-forming materials, disintegrants such as Ad-Di-Sol, Explotab, Pregelatinized starches, crospovidone NF and other materials known to the formulation art can be incorporated into the matrix as fine powder or beadlets.

Any sort of particle can be used in this formulation, so long as it contains or comprises one or more beneficial agents, is stable in the matrix-forming material during

manufacturing and storage, and has sufficient size and definition in terms of shape and color so that it is visible in the matrix. Colored beadlets, as described below are most preferred.

The term "beneficial agent" means any compound or material which acts on a mammal in one fashion or another when consumed for its intended use in the manner prescribed. For example, a drug is a beneficial agent for the purposes of this definition. But in addition there are numerous other compounds which can have a subjective or objective beneficial effect on the user and which are to be included within the meaning of this term. For example an antacid or anti-gas agent can have a beneficial effect when used to treat indigestion. A breath freshener provides an objective and a subjective beneficial effect to many people. Nutritional agents such as vitamins, minerals, or amino acid supplements are beneficial to those needing to supplement their diet. Flavors and sweeteners provide a subjective benefit and a source of energy as well, and are also included. These examples illustrate but a few of the many different kinds of materials which are intended to be included within the scope of the term beneficial agent. Others will be apparent to the practitioner of this art.

Drugs and drug delivery are of greatest interest herein. The word "drug" is used in its broadest sense and includes any agent which exhibits a pharmacological effect on the user and which can be administered via SGC technology utilizing particles as described herein. Any solid or liquid form of a drug can be used provided it can be manufactured into a particulate, as is true for any compound which constitutes a beneficial agent for the purposes of this invention. Both fat soluble and water soluble drugs may be used. Drugs for treating cough, cold, and allergy symptoms are of most interest. They include antihistamines; drugs for treating inflammation, pain and pyrexia; nasal decongestants; expectorants; sedatives as used in cough and cold remedies, and the like. Phenylpropanolamine hydrochloride, caramiphen edisylate, acetaminophen, aspirin or another non-steroidal anti-inflammatory, pseudoephrine hydrochloride, dextromethorphan hydrobromide, and chlorpheniramine maleate are most preferred.

In so far as particle size is concerned, the principal consideration that of creating a particle of a size such that they are visible to the naked eye through the matrix under normal lighting conditions. Beadlet size can vary in any given capsule. Preferred beadlets will have a diameter in the range of about 149 to 1190 microns. The most preferred particle size is between about 420 and 840 microns microns (about 20-40 mesh). Particle size can vary in a given preparation or particles of different narrow ranges can be confected and these final products mixed to provide a choice of preparations with different particle sizes.

Particles can be comprised of pure agent or, as will more often be the case, the agent can be coated with a protective layer which may or may not affect how fast the particle dissolves and releases the active ingredient. Creating particles of pure agent is mostly a matter of shaping the raw material by some means, usually a mechanical means. A coating of some sort may be added to protect the neat compound. More often than not, one will want

to coat the particles for both functional and aesthetic reasons. There are a number of ways to coat particles. Pan coating, for example, is a well established technology that provides a basic pellet. A more sophisticated approach is to create a core and then to add one or more layers of a coating to the core. If the "seeds" are differentially coated, that is some have a thicker coating layer, any particles with different coating thicknesses are loaded into one capsule, drug can be delivered over an extended period to time. This technology was pioneered by R. H. Blythe in U.S. patent 2,738,303. He describes there a therapeutic preparation in unit dosage form prepared from non-pariel seeds (sugar pellets), screened, placed in a coating pan, wetted with syrup, then treated with a 80:20 mixture of dextro-amphetamine sulfate and calcium sulfate dihydrate, then dried. This process was repeated several times to build up drug on the non-pariel seed; it is treated with talc to create the core pellet. These pellets were then treated with a wax-fat coating solution one or more times to create pellets with one or more fatty layers surrounding the core pellet. Later developments include placing an osmotic wall around the core pellet, and preparations where the drug dissolves in the wall-forming material of the particle and passes through it to the exterior on exposure to water. Reference to such particles can be found in the literature, for example in U.S. patent 4,434,153; the relevant parts are incorporated herein by reference. See also U.S. patent 4,961,932 which contains a substantial list of patents said to relate to tiny or small pills, and dosage forms comprising same.

Particles can be prepared in a single color, or in different colors if desired. Dyes and lakes of any sort may be used so long as they are not toxic or do not have an untoward or deleterious effect on the user. For example blue particle could be prepared for use with a translucent white wax lozenge. Or red, white and blue beadlets could be incorporated into a sorbitol base to provide an aesthetically pleasing lozenge.

Particle stability, as compared with stability of the active agent, is another factor which must be taken into consideration. Particles must remain chemically and physically stable under the conditions used to manufacture troches. Furthermore, particle and matrix must not undergo some kind of chemical or physical interaction once manufactured. It is not possible to identify or define all of the conditions or combinations which could lead to particle-matrix interactions. However, particulates coatings known to be soluble in sorbitol or corn syrup should not be used to formulate coated beads where such sugars are the intended matrix-forming agent.

Stability of the beneficial agent is a consideration as well, just as it is with any formulation, not just these preparations. There is no single recipe for formulating a product which will not degrade chemically. Each formulation must be addressed on a case-by-case basis; this is within the skill of one trained in the formulation arts.

In so far as manufacturing is concerned, there are no limitations placed on the practice of this invention. Lozenges, for example, are commonly manufactured by preparing a candy

base by combining ingredients and cooking the mix, with or with out stirring, to create the stock from which the lozenge will be prepared. Then a portion of this mix which is held at an elevated temperature to keep it liquid is used as a diluent; particles are added to the liquid mix with stirring to create a dispersion. This material is poured into molds, cooled and packaged.

Alternatively, products may be made by injection molding techniques. This approach is particularly useful where waxes are used as the matrix-forming agent. A heated mixture of wax and particles is passed through an injection molding apparatus in such as manner as to fill mold and allow for cooling of the product during the manufacturing cycle. Or a premixed stream of room temperature material is processed under pressure into molds to eliminate the need for a cooling step. As a third alternative, a feed stock of matrix-forming material can be mixed with a feed-stock stream of particles, passed through a mixing device and injected into a mold to form the final product. Other injection molding processes are considered to be within the purview of this invention.

Finished product may be packaged without any special handling precautions. The usual considerations such as the need to exclude moisture or ultraviolet light should be taken into consideration. While it is preferred to package the product in such as way as to allow the consumer to view the contents and the particles in the matrix before opening the package, the invention can be practiced within the context of packaging the product in opaque jar or overwrap.

Any form or shape can be used in this invention. Troches or lozenges may be uniform in shape such as is the case for an oval, square, rectangular, or have multiple sided presentation. Geometric forms can be used. Shapes representing persons or things, either real or imagined can be prepared, especially when injection molding techniques are used. Shape and form are limited only by the imagination of the practitioner.

The following examples are provided to illustrate the invention. They are not to be read as limiting the invention in any manner.

Examples

Example 1

Preparation of Wax Matrix Caplets Containing Beadlets

A required amount of white wax was taken into a glass beaker and heated in an oil bath until the wax melted using a hot plate. Beadlets obtained from Central Pharmaceuticals, Inc. Seymour, Indiana, were poured into the molten wax and stirred with a spatula to obtain a homogenous suspension. The molten wax/bead suspension was carefully poured into molds and allowed to cool and form hard caplets. These caplets were then pushed out of the molds.

The active ingredients in the beadlets were chlorpheneramine maleate 12.0 mg and phenylpropanolamine HCl 75.0 mg. These beadlets were differentially coated so that some beadlets would release the actives immediately, and others would release their active

ingredients at several time points over a 12 hour period.

Example 2

Preparation of Clear Lozenge Matrix Caplets Containing Beadlets

Prototypes of clear lozenge matrix caplets containing beadlets were prepared as follows:

A required amount of sorbitol (70% solution) and lycasin mixture in a ratio of 96:4 was added to a steam jacketed cooker and cooked until all the water had evaporated. Then vacuum was applied to the vessel and cooking continued until all bubbles had disappeared in the liquid candy dispersion. This molten candy mass was emptied into a stainless steel container and stored in an oven at 110° C. A required amount of candy base was transferred into a glass beaker and placed under a mechanical stirrer. Beads obtained from Central Pharmaceuticals, Inc. Seymour, Indiana, were poured into the candy base and stirred to obtain a homogenous suspension. Candy base/bead suspension was seeded with few crystals of sorbitol (Neosorb) and carefully poured into the molds. Molds were placed in an oven at 40° C and allowed to cool and form hard caplets. These caplets were then pushed out of the molds.

The active ingredients in the beadlets were chlorpheneramine maleate 12.0 mg and phenylpropanolamine HCl 75.0 mg. These beadlets were differentially coated so that some beadlets would release the actives immediately, and others would release their active ingredients at several time points over a 12 hour period.

Claims:

1. A pharmaceutically acceptable preparation comprising at least one pharmaceutically acceptable transparent or semi-transparent solid matrix-forming material in which are entrapped small particles which contain at least one beneficial agent.

2. The preparation of claim 1 wherein matrix-forming material is a wax or an edible sugar and said particles are beadlets having diameters between about 149 and 1190 microns.

3. The preparation of claim 2 wherein the beneficial agent is a drug.

4. The preparation of claim 3 wherein the beadlets are time released or immediate release beadlets which contain medicaments for treating cough, cold and/or allergy symptoms.

5. The preparation of claim 1 wherein the beadlets are time released or immediate release beadlets which contain medicaments for treating cough, cold and/or allergy symptoms.

6. A process for manufacturing the preparation of claim 1 which process comprises using injection molding.

7. The process of claim 6 wherein the matrix-forming material is a wax.

8. The process of claim 7 where the preparation contains beadlets which are disintegrating or non-disintegrating.

9. The process of claim 7 wherein the preparation comprises at least one wax as the matrix-forming material and the particles are beadlets comprising time released or immediate release beadlets which contain medicaments for treating cough, cold and/or allergy symptoms.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/07817

A. CLASSIFICATION OF SUBJECT MATTER

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US CL :424/469

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/439-441; 514/849, 850, 787

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,649,043 (URQUHART) 10 March 1987, see Figures 2, 3, column 4 lines 18-40.	1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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